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(57) Abstract

A method is described which permits the release of a pharmaceutical product having weakly basic characteristics so as to be very soluble in an acid pH and virtually insoluble in a basic pH, at a constant rate, independently of the pH conditions in which the pharmaceutical product and the pharmaceutical form obtained from the latter are found. The method consists in the preparation of pellets composed of an active principle, a swellable polymeric material and a gastroresistant polymeric material. By carrying these pellets in a natural or synthetic polymeric material which is gellable and hydrophilic, or in a lipophilic polymeric or non-polymeric material, it is possible to obtain modified-release pharmaceutical forms which are capable of releasing the active principle at the same rate both in an acidic environment and in a basic environment.

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METHOD FOR THE PREPARATION OF PROLONGED-RELEASE ORAL PHARMACEUTICAL FORMS CONTAINING ACTIVE SUBSTANCES HAVING A SOLUBILITY DEPENDENT UPON THE PH VALUE

The present invention relates to oral pharmaceutical formulations containing active principles having weak basic characteristics.

In particular, the formulations forming the subject of the invention permit the release of the active principle in a manner independent of the variations of the pH of the gastrointestinal tract.

The prolonged administration, by the oral route, of basic pharmaceutical products which may exhibit very significant variations of solubility depending on the variations of pH which are specific to the gastrointestinal tract, is a problem which has been recognised for some time.

This dependence of the rate of solubilisation upon the pH value of the medium proves to be one of the most difficult problems to resolve when it is necessary to design or to produce prolonged-release pharmaceutical forms.

In this specific case, in fact, basic or weakly basic pharmaceutical products are characterised by a high rate of solubilisation in a gastric (acidic) environment and by a dramatic reduction in the solubility in an intestinal (alkaline) environment.

In order to overcome these disadvantages, a multiplicity of proposals have been put forward:

a - the formation of floating systems in an acidic environment capable of ensuring the persistence of

the preparation in the gastric environment where the active principle is soluble as described in US No. 4,126,672 (21/11/1978);

b - the incorporation in the pharmaceutical form of ancillary substances (excipients and technological coadjuvants) capable of slowing down gastric evacuation and thus able to cause the pharmaceutical form for a greater period of time to persist in the zone of high solubility of the active principle. Systems of this type are described in Drug Dev. Ind. Pharm. 10, 527, 1984 and in Int. J. Pharm. 12, 315, 1982;

c - the formation of systems adherent in an acidic environment (gastric bioadherent systems) with the objective, in this case also, of increasing the persistence of the pharmaceutical form in an environment having an acidic pH, as described, for example, in J. Pharm. Sci. 74, 399, 1985 and in Int. J. Pharm. 19, 107, 1984;

d - the carrying in the pharmaceutical form of buffering substances which are capable of maintaining around the pharmaceutical form, once in contact with the fluids of the gastrointestinal tract, an acidic microenvironment such as to facilitate and in any event not to slow down the dissolving of the active principle; systems of this type are described in EP A 0,032,562 A1 and in Int. J. Pharm. 50, 223, (1989).

However, all these systems exhibit numerous limitations and encounter significant difficulties either on account of the complexity in the

standardisation of the preparation or since, in vivo, the system under consideration does not behave as foreseen by the in vitro tests. In fact, the physiological factors (housekeeper wave) may profoundly modify the performance levels of the pharmaceutical form or of the system under consideration, especially in respect of the differing conditions of the patient (whether or not under fasting conditions).

The invention proposes modified-release pharmaceutical forms which are capable of releasing a basic active principle in a manner independent of the values of the pH within the range which is encountered in the gastrointestinal tract.

It has now been found that the incorporation of the basic active principle in modified-release pellets composed of a complex polymer matrix formed of a water-insoluble and swelling phase and of a gastroresistant, but enterosoluble phase, permits a slowing down of the high dissolution rate of the active principle in the gastric environment, and a very significant increase in the dissolution rate in the intestinal environment.

The modified-release pellets may be mixed with a polymer material, obtaining matrices from which the basic active principle (whose dissolution rate at the various pH values has been "standardised"), is released in a prolonged manner, without the releasing rate being substantially affected by the change of pH.

Thus, an object of the invention is provided by pharmaceutical formulations which permit the release, in a manner which is prolonged and independent of the pH of the entire gastrointestinal tract, of an active

principle having a weakly basic character. A further object of the invention is a process for the preparation of said pharmaceutical formulations.

Examples of active principles which may conveniently be formulated according to the present invention comprise dipyridamole, ketanserin and cinnarizine.

The phase which is insoluble in water and swellable therein is a polymer selected from among the so called dispersants and "superdispersants", preferably from among crosslinked sodium carboxymethylcellulose, crosslinked polyvinyl-pyrrolidone, carboxymethyl starch, potassium methacrylate-divinylbenzene copolymer, polyvinyl alcohols, derivatives of dextran, glucans, starches, modified starches, derivatives of cellulose; crosslinked sodium carboxymethylcellulose is particularly preferred. Such materials are characterised in that, being formulated also in the form of mixtures in tablets, they exhibit very hydrophilic properties and encounter a rapid interaction with water and/or aqueous solutions which cause a swelling with development of a pressure which can be measured using the apparatus described in Eur. Pat. 89104430.7.

The gastroresistant phase is a polymer selected from cellulose acetate phthalate, cellulose acetate propionate, cellulose acetate trimellitate, zein, acrylic and methacrylic polymers and copolymers and their derivatives; cellulose acetate trimellitate and cellulose acetate phthalate are particularly preferred.

The pellets are subsequently carried in a gellable hydrophilic matrix or in a lipophilic matrix, which is capable of controlling the release of the active principle for a prolonged period of time.

The gellable hydrophilic matrix may be composed of hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, xanthans, natural or synthetic rubbers, carboxyvinyl polymers, scleroglucans, mannans, galactomannans, chitin and chitosans, preferably hydroxypropylmethylcellulose.

The lipophilic matrix may be composed of mono-, bi- and trisubstituted natural and synthetic glycerides, or high molecular weight fatty acids.

The compositions of the invention may be obtained by various processes, as will be described in the examples which will be given hereinbelow.

A first process is that of solubilisation in an organic solvent or in a mixture of organic solvents, preferably of low polarity, of the active principle and the enterosoluble polymeric material.

The polymeric material which swells rapidly and is insoluble in water and which, normally, also proves to be insoluble or poorly soluble in the organic solution is added to the solution obtained; thus, a suspension is obtained, which is stirred for 10 30 minutes.

The solvent is then evaporated under reduced pressure by means of a rotary evaporator (loading) or some other suitable apparatus at a temperature below 100°C and related to the type of solvent and to the physicochemical properties of the active principle and to the operational conditions under which the process

of evaporation-concentration takes place.

A pasty residue is obtained, from which the residual traces of solvent are eliminated via suitable processes (heating in a heater with air circulation or under vacuum, evaporation in a rotary dryer under vacuum etc.) to obtain a solid product which may be a granulate or a vitreous or pasty mass which may be subjected to a grinding and/or crushing process in accordance with the known conventional technological processes.

This gives a granular product which is composed of the following three components:

a - Active principle

b - Polymeric material which is insoluble in water and which rapidly swells in contact with an aqueous medium (superdispersant)

c - Enterosoluble and gastroresistant polymeric material.

The ratios in which the various components may be present in the mixture are not critical and may vary for all three components within very wide ranges, between 5 and 90%. A preferred ratio between the constituents a), b) and c) and the polymeric material constituting the matrix is equal to approximately 1:2:1:1, respectively.

The pharmaceutical form may also contain other known excipients.

The loading of the active principle and of the gastroresistant and enterosoluble polymeric material may also be effected via various processes such as that of fluidisation or of spray drying.

In the case of fluidisation, the polymeric material which is insoluble and which rapidly swells in water is placed in the containing vessel of a fluidised-bed apparatus (of the Glatt, Aeromatic etc. type) and, following the application of the air flow, is brought to the fluidised condition at a temperature which may vary from ambient temperature to approximately 60-70°C, the organic solution of the active principle and of the enterosoluble polymer is sprayed onto the moving material. The active principle and the enterosoluble polymer may be dissolved in various solvents and may be loaded separately onto the hydrophilic material. The selection of the solvent or of the mixture of solvents to be utilised will be determined by the solubility characteristics of the active principle and of the polymeric material employed and by the safety requirements relating to the management of the plant and by the physicochemical and organoleptic properties of the finished product; said properties must comply with the standards which, with precise definitions and limits, are set out by the Health Authorities in the case where an active principle is intended for formulation into a pharmaceutical form for human or veterinary use.

The process of spraying the solution of the mixture of enterosoluble polymeric material and active principle is carried out at a controlled temperature depending on the characteristics both of the solvent and of the active principle. For the loading, it is possible to use other techniques such as moistening and granulation, topogranulation, spherogranulation,

rotogranulation and extrusion.

Proceeding as indicated above, the result is a loading of the active principle and of the enterosoluble polymer on the surface of the individual particles of the superdispersant polymeric material which is used as carrier.

The loaded product exists in the form of a flowing granular material which may be subjected to further known processes, for the preparation of suitable administration forms.

In the formulation of modified-release pharmaceutical forms, it is also possible to use other technological coadjuvants which are capable of imparting suitable technological properties to the mixture for the formation of the pharmaceutical forms.

By the above methods, it is possible to obtain pharmaceutical forms which are capable of releasing "in vitro" the active principle at a rate which is no longer determined by the pH value, as will be described in greater detail in the examples given hereinbelow.

By utilising the granular material thus obtained, it is also possible to obtain pulsed-release (or sustained-release) pharmaceutical forms by preparing, for example, two-layer tablets in which the first layer is obtained by using a conventional granulate, from which the active principle will be released rapidly and completely within the stomach, while the second layer containing the modified granulate, prepared in accordance with the invention, on its own or in combination with gellable polymers, will release the active principle at a later stage, irrespective of the

pH value in which the pharmaceutical form is found.

Using the granulates thus described (conventional granulate and modified-release granulate), it is furthermore possible to produce different tablets which are introduced, in the same or a different number, depending upon the therapeutic requirements, into a hard gelatin capsule.

To control the rate of dissolving "in vitro", it is possible to use the processes and the apparatuses which are usually employed for these types of controls, such as, for example, the apparatus described in USP, edition XXII.

In order to give a more precise statement of the features of the invention, certain embodiments will now be described.

Even though the examples which follow refer to the pharmaceutical use alone and to the preparation of pharmaceutical forms such as tablets, the invention may also be used for the preparation of other types of pharmaceutical forms (such as, for example: capsules containing powders and granular products obtained in accordance with the process indicated) or in other sectors of technology, in which it is desired to obtain the release of an active substance at a constant rate under differing pH conditions of the environment.

EXAMPLE 1

A preliminary study was carried out for the purpose of assessing the dissolution rate of the basic pharmaceutical product dipyridamole in an acid medium (simulated gastric fluid USP XXII, without enzyme component) at pH 1.2, and in an alkaline medium

(simulated intestinal fluid USP XXII, without enzyme component), at pH 7.5.

The apparatus used for the test is that described in USP XXII (2-paddle apparatus), using 1000 ml of fluid, at 37°C and stirring at 100 rpm.

The pharmaceutical product was determined by spectrophotometry (Spectracomp, Advanced Product, Mi, I), using a wavelength of 283 nm for the determinations in gastric fluid, and of 294 nm for those in intestinal fluid.

The results of the dissolving tests are set out in the following tables.

Time (min)	Dipyridamole % (pH 1.2)
0	0
0.50	46.5
1.00	89.9
1.50	96.5
2.00	100.0

Time (min)	Dipyridamole % (pH 7.5)
0	0
15	2.0
30	4.0
60	5.5
120	5.9
180	6.1
240	6.3

EXAMPLE 2

Modified-release pellets based on dipyridamole:

Composition:

Dipyridamole (Recordati, MI, I)	50 g
Cellulose acetate trimellitate (Eastman® C-A-T, Eastman Chem. Prod. Inc., Kingsport, TN, USA)	100 g
Crosslinked sodium carboxymethylcellulose (Ac-Di-Sol®, FMC Corp. Philadelphia, PA, USA)	50 g

Preparation:

100 grams of cellulose acetate trimellitate are dissolved in 1000 ml of a 3:1 acetone-ethanol 95° mixture, and to the solution is added a solution of 50 g of dipyridamole in 200 ml of 95° ethanol, giving a complete solution of yellow colour.

50 g of crosslinked sodium carboxymethyl cellulose are then added, giving a suspension which is evaporated under vacuum, using a Rotavapor (Buchi R 110, Flawil, CH), at approximately 40-45°C, to obtain a residue, which is fluid but very viscous, of yellow colour, which is poured onto an extensive surface, so as to obtain a relatively thin layer.

The material is left in a heater with air circulation (60°C) for 24 hours and then in a dryer, so as to obtain a solid residue, which is ground using a plate mill, giving a powder product which is screened (ASTM series screens, Endecotts, London, UK), separating the following two particle-size fractions: 63-250 µm, and 250-500 µm.

The dissolving test was carried out on the

modified-release pellets of both the particle-size fractions, using the apparatus according to USP XXII no. 2 (paddle; see Example 1).

The test was carried out on a sample of powders equal to 100 mg of active principle in 1000 ml of simulated gastric fluid (pH 1.2) and 1000 ml of simulated intestinal fluid (pH 7.5), using the conditions and the apparatus which have been described in Example 1.

The results obtained are set out in the following tables, as compared with those for the active principle alone.

Particle-size fraction 63-250 µm (pH 1.2)

Time (min)	Dipyridamole from modified-release pellets (%)	Dipyridamole (%)
0	0	0
2		100.0
3	32.0	
6	61.7	
12	75.1	
24	84.8	
45	90.8	
60	92.7	
90	94.8	
120	96.3	

Particle-size fraction 250-500 µm (pH 1.2)

Time (min)	Dipyridamole from modified-release pellets (%)	Dipyridamole (%)
0	0	0
2		100.0
3	14.2	
6	28.7	
12	44.8	
24	61.0	
45	73.5	
60	78.6	
90	84.0	
120	87.0	

Particle-size fraction 63-250 µm (pH 7.5)

Time (min)	Dipyridamole from modified-release pellets (%)	Dipyridamole (%)
0	0	0
3	37.5	
6	62.2	
12	79.4	
18	86.0	
24	90.0	
30	92.8	4.0
45	97.7	4.8
60	100.0	5.6

Particle-size fraction 250-500 μm (pH 7.5)

Time (min)	Dipyridamole from modified-release pellets (%)	Dipyridamole (%)
0	0	0
3	8.6	
6	19.7	
12	44.0	
18	56.4	
24	63.8	
30	68.8	4.0
45	76.0	4.8
60	80.5	5.6

EXAMPLE 3

Starting from the modified-release pellets, particle-size fraction 63-250 μm prepared in accordance with Example 2, tablets were obtained with modified release of 100 mg of dipyridamole, each having the following composition:

Dipyridamole (Recordati, MI, I, batch no. 88512/348)	100 mg
Cellulose acetate trimellitate (Eastman® C-A-T, Eastman Chem. Prod. Inc. Kingsport, TN, USA)	200 mg
Crosslinked sodium carboxymethylcellulose (Ac-Di-Sol®, FMC Corp., Philadelphia, PA; USA)	100 mg
Hydroxypropylmethylcellulose (Methocel® K4M, Colorcon, Orpington, UK)	100 mg
Magnesium stearate (Carlo Erba, MI, I)	5 mg
Colloidal silica (Syloid® 244, Grace, GmbH	

Worms, D) 2 mg

The granular material of Example 2 is intimately mixed with the hydroxypropylmethylcellulose in a Turbula mixer (type T2A, W.A. Bachofen, Basel, CH) for 15 minutes, and is then added to and mixed (for 5 minutes) with magnesium stearate and colloidal silica, to give a homogeneous mixture which is readily flowable.

Convex tablets, 12 mm in diameter, were prepared on a Korsch EKO reciprocating tableting machine (Berlin, D), and were then subjected to the dissolution test in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.5), using the apparatus and under the conditions described in Example 1.

The results obtained are set out in the following table.

Time (min)	Dipyridamole % released at pH 1.2	Dipyridamole % released at pH 7.5
0	0	0
30	9.2	6.1
60	13.0	9.0
120	18.8	12.9
360	35.6	22.2
600	49.1	30.2
900	65.6	48.3
1200	82.3	58.4
1440	96.1	67.0

EXAMPLE 4

Starting from the modified-release pellets, particle-size fraction 63-250 µm, prepared in

Example 2, tablets were obtained with prolonged release of 100 mg of dipyridamole, each having the following composition:

Dipyridamole (Recordati MI, I, batch no. 88512/348)	100 mg
Cellulose acetate trimellitate (Eastman® C-A-T, Eastman Chem. Prod. Inc., Kingsport, TN, USA)	200 mg
Crosslinked sodium carboxymethylcellulose (Ac-Di-Sol®, FMC Corp., Philadelphia, PA, USA)	100 mg
Hydroxypropylmethylcellulose (Methocel® K4M, Colorcon, Orpington, UK)	107 mg
Mannitol (Carlo Erba, MI, I)	27 mg
Magnesium stearate (Carlo Erba, MI, I)	5 mg
Colloidal silica (Syloid® 244, Grace, GmbH, Worms, D)	2 mg

The granular material of Example 2 is intimately mixed with the hydroxypropylmethylcellulose in a Turbula mixer (type T2A, W.A. Bachofen, Basel, CH) for 15 minutes, and is then added to and mixed (for 5 minutes) with magnesium stearate and colloidal silica, giving a homogeneous mixture which is readily flowable.

Convex tablets, 12 mm in diameter, were prepared on a Korsch EKO reciprocating tableting machine (Berlin, D), and were then subjected to the dissolution test in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.5), using the apparatus and under the conditions described in Example 1.

The results obtained are set out in the following

table.

Time (min)	Dipyridamole % released at pH 1.2	Dipyridamole % released at pH 7.5
0	0	0
30	12.0	16.1
60	19.1	23.1
120	27.7	29.6
360	49.3	42.8
600	65.5	51.5
900	83.3	66.1
1200	95.3	82.9
1440	99.9	95.7

EXAMPLE 5

Starting from the modified-release pellets, particle-size fraction 63-250 µm, prepared in Example 2, tablets were obtained with prolonged release of 100 mg of dipyridamole, each having the following composition:

Dipyridamole (Recordati MI, I, batch no. 88512/348)	100 mg
Cellulose acetate trimellitate (Eastman® C-A-T, Eastman Chem. Prod. Inc., Kingsport, TN, USA)	200 mg
Crosslinked sodium carboxymethylcellulose (Ac-Di-Sol®, FMC Corp., Philadelphia, PA, USA)	100 mg
Hydroxypropylmethylcellulose (Methocel® K4M, Colorcon, Orpington, UK)	80 mg
Mannitol (Carlo Erba, MI, I)	53 mg
Magnesium stearate (Carlo Erba, MI, I)	5 mg

Colloidal silica (Syloid® 244, Grace, GmbH, Worms, D) 2 mg

The granular material set out in Example 2 is intimately mixed with the hydroxypropylmethylcellulose in a Turbula mixer (type T2A, W.A. Bachofen, Basel, CH) for 15 minutes, and is then added to and mixed (for 5 minutes) with magnesium stearate and colloidal silica, giving a homogeneous mixture which is readily flowable.

Convex tablets, 12 mm in diameter, were prepared on a Korsch EKO reciprocating tableting machine (Berlin, D), and were then subjected to the dissolution test in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.5), using the apparatus and under the conditions described in Example 1.

The results obtained are set out in the following table.

Time (min)	Dipyridamole % released at pH 1.2	Dipyridamole % released at pH 7.5
0	0	0
30	38.2	28.1
60	51.5	40.5
120	67.0	53.9
240	84.6	69.8
360	93.3	79.0
480	96.4	84.5
600	97.5	88.1
720		90.3

EXAMPLE 6

Modified-release pellets

Composition:

Dipyridamole (Recordati, MI, I	50 g
Cellulose acetate phthalate (Eastman® C-A-P™ Eastman Chem. Prod., Inc., Kingsport, TN, USA)	100 g
Crosslinked sodium carboxymethylcellulose (Ac-Di-Sol®, FMC Corp., Philadelphia, PA, USA)	50 g

Preparation:

100 grams of cellulose acetate phthalate are dissolved in 1000 ml of 2:1 acetone-ethanol 95° mixture, and to the solution is added a solution of 50 g of dipyridamole in 200 ml of 95° ethanol, giving a complete solution of yellow colour.

50 g of crosslinked sodium carboxymethylcellulose are then added, giving a suspension which is evaporated under vacuum, using a Rotavapor (Buchi R 110, Flawil, CH), at approximately 40-45°C, so as to obtain a residue, which is fluid but very viscous, of yellow colour, which is poured onto an extensive surface, so as to obtain a relatively thin layer.

The material is left in a heater with air circulation (60°C) for 24 hours, and then in a dryer, so as to obtain a solid residue, which is ground using a plate mill, giving a powder product which is screened (ASTM series screen, Endecotts, London, UK), separating the following two particle-size fractions: 63-250 µm and 250-500 µm.

The dissolution test was carried out on the

modified-release pellets of both the particle-size fractions, using the apparatus according to USP XXII no. 2 (paddle).

The test was carried out on a sample of powders corresponding to 100 mg of active principle in 1000 ml of simulated gastric fluid (pH 1.2) and 1000 ml of simulated intestinal fluid (pH 7.5), under the conditions and using the apparatus described in Example 1.

The results obtained are set out in the following tables, compared with those for the active principle alone.

Particle-size fraction 63-250 µm (pH 1.2)

Time (min)	Dipyridamole from modified-release pellets (%)	Dipyridamole (%)
0	0	0
2		100.0
3	27.5	
6	56.1	
12	69.6	
24	78.2	
45	83.9	
60	86.3	
90	88.7	
120	90.6	

Particle-size fraction 250-500 µm (pH 1.2)

Time (min)	Dipyridamole from modified-release pellets (%)	Dipyridamole (%)
0	0	0
2		100.0
3	15.5	
6	31.0	
12	43.0	
24	55.0	
45	66.0	
60	70.0	
90	76.0	
120	80.0	

Particle-size fraction 63-250 µm (pH 7.5)

Time (min)	Dipyridamole from modified-release pellets (%)	Dipyridamole (%)
0	0	0
3	35.5	
6	63.7	
12	81.4	
18	88.3	
24	92.1	
30	94.8	4.0
45	98.0	4.8
60	100.0	5.6

Particle-size fraction 250-500 μm (pH 7.5)

Time (min)	Dipyridamole from modified-release pellets (%)	Dipyridamole (%)
0	0	0
3	15.0	
6	31.7	
12	53.2	
18	66.2	
24	74.2	
30	79.6	4.0
45	88.1	4.8
60	93.3	5.6

EXAMPLE 7

Starting from the modified-release pellets, particle-size fraction 63-250 μm, prepared in Example 6, tablets were obtained with modified release of 100 mg of dipyridamole, each having the following composition:

Dipyridamole (Recordati MI, I, batch no. 88512/348)	100 mg
Cellulose acetate phthalate (Eastman® C-A-P™, Eastman Chem. Prod. Inc., Kingsport, TN, USA)	200 mg
Crosslinked sodium carboxymethylcellulose (Ac-Di-Sol®, FMC Corp., Philadelphia, PA, USA)	100 mg
Hydroxypropylmethylcellulose (Methocel® K4M, Colorcon, Orpington, UK)	100 mg
Magnesium stearate (Carlo Erba, MI, I)	5 mg
Colloidal silica (Syloid® 244, Grace,	

GmbH, Worms, D) 2 mg

The granular material of Example 6 is intimately mixed with the hydroxypropylmethylcellulose in a Turbula mixer (type T2A, W.A. Bachofen, Basel, CH) for 15 minutes and is then added to and mixed (for 5 minutes) with magnesium stearate and colloidal silica, giving a homogeneous mixture which is readily flowable.

Convex tablets, 12 mm in diameter, were prepared on a Korsch EKO reciprocating tableting machine (Berlin, D), and were then subjected to the dissolving test in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.5), using the apparatus and under the conditions described in Example 1.

The results obtained are set out in the following table.

Time (min)	Dipyridamole % released at pH 1.2	Dipyridamole % released at pH 7.5
0	0	0
30	6.8	6.8
60	10.2	10.4
120	16.2	14.5
360	31.6	24.2
600	42.3	30.7
900	52.5	41.6
1200	64.0	51.8
1440	76.3	56.2

EXAMPLE 8

Starting from the modified-release pellets, particle-size fraction 63-250 µm, prepared in Example

6, tablets were obtained with prolonged release of 100 mg of dipyridamole, each having the following composition:

Dipyridamole (Recordati MI, I, batch no. 88512/348)	100 mg
Cellulose acetate phthalate (Eastman® C-A-P™, Eastman Chem. Prod. Inc., Kingsport, TN, USA)	200 mg
Crosslinked sodium carboxymethylcellulose (Ac-Di-Sol®, FMC Corp., Philadelphia, PA, USA)	100 mg
Hydroxypropylmethylcellulose (Methocel® K4M, Colorcon, Orpington, UK)	107 mg
Mannitol (Carlo Erba, MI, I)	27 mg
Magnesium stearate (Carlo Erba, MI, I)	5 mg
Colloidal silica (Syloid® 244, Grace, GmbH, Worms, D)	2 mg

The granular material of Example 6 is intimately mixed with the hydroxypropylmethylcellulose in a Turbula mixer (type T2A, W.A. Bachofen, Basel, CH) for 15 minutes and is then added to and mixed (for 5 minutes) with the magnesium stearate and the colloidal silica, giving a homogeneous mixture which is readily flowable.

Convex tablets, 12 mm in diameter, were prepared on a Korsch EKO reciprocating tableting machine (Berlin, D), and were then subjected to the dissolution test in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.5), using the apparatus and under the conditions described in Example 1.

The results obtained are set out in the following

table.

Time (min)	Dipyridamole % released at pH 1.2	Dipyridamole % released at pH 7.5
0	0	0
30	12.7	21.5
60	19.9	28.2
120	29.5	34.7
360	49.9	48.6
600	61.4	58.5
900	71.1	74.3
1200	78.3	93.9
1440	84.0	99.8

EXAMPLE 9

Starting from the modified-release pellets, particle-size fraction 63-250 µm, prepared in Example 6, tablets were obtained with prolonged release of 100 mg of dipyridamole, each having the following composition:

Dipyridamole (Recordati MI, I, batch no. 88512/348)	100 mg
Cellulose acetate phthalate (Eastman® C-A-P™, Eastman Chem. Prod. Inc., Kingsport, TN, USA)	200 mg
Crosslinked sodium carboxymethylcellulose (Ac-Di-Sol®, FMC Corp., Philadelphia, PA, USA)	100 mg
Hydroxypropylmethylcellulose (Methocel® K4M, Colorcon, Orpington, UK)	80 mg
Mannitol (Carlo Erba, MI, I)	53 mg
Magnesium stearate (Carlo Erba, MI, I)	5 mg

Colloidal silica (Syloid® 244, Grace, GmbH, Worms, D) 2 mg

The granular material of Example 6 is intimately mixed with the hydroxypropylmethylcellulose in a Turbula mixer (type T2A, W.A. Bachofen, Basel, CH) for 15 minutes, and is then added to and mixed (for 5 minutes) with magnesium stearate and colloidal silica, giving a homogeneous mixture which is readily flowable.

Convex tablets, 12 mm in diameter, were prepared on a Korsch EKO reciprocating tableting machine (Berlin, D), and were then subjected to the dissolving test in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.5), using the apparatus and under the conditions described in Example 1.

The results obtained are set out in the following table.

Time (min)	Dipyridamole % released at pH 1.2	Dipyridamole % released at pH 7.5
0	0	0
30	41.0	24.5
60	54.0	31.6
120	69.1	39.6
360	78.7	56.9
600	89.0	68.2
900	91.5	78.3
1200	93.0	81.6
1440	94.1	90.8

CLAIMS

1. Oral pharmaceutical formulations containing active principles having weak basic characteristics, comprising pellets composed of active principle, a swellable polymeric material and a gastroresistant polymeric material, which are carried in a gellable hydrophilic matrix or in a lipophilic matrix.

2. Pharmaceutical formulations according to Claim 1, in which the active principle is selected from dipyridamole, cinnarizine and ketanserin.

3. Pharmaceutical formulations according to Claim 1 or 2, in which the swellable polymeric material is selected from crosslinked sodium carboxymethylcellulose, crosslinked polyvinyl-pyrrolidone, carboxymethyl starch, potassium methacrylate-divinylbenzene copolymer, polyvinyl alcohols, derivatives of dextran, glucans, starches, modified starches and cellulose derivatives.

4. Pharmaceutical formulations according to any one of the preceding claims, in which the gastroresistant polymeric material is selected from cellulose acetate phthalate, cellulose acetate propionate, cellulose acetate trimellitate, zein, acrylic and methacrylic polymers and copolymers and their derivatives.

5. Pharmaceutical formulations according to any one of the preceding claims, in which the pellets are carried in a gellable hydrophilic matrix.

6. Pharmaceutical formulations according to Claim 5, in which the gellable hydrophilic matrix is composed of hydroxypropylcellulose, hydroxypropylmethylcellulose,

methylcellulose, xanthans, natural or synthetic rubbers, carboxyvinyl polymers, scleroglucans, mannans, galactomannans, chitin and chitosans.

7. Pharmaceutical formulations according to any one of Claims 1-5, in which the pellets are carried in a lipophilic matrix.

8. Pharmaceutical formulations according to Claim 7, in which the lipophilic matrix is composed of mono-, bi- and trisubstituted natural and synthetic glycerides, or high molecular weight fatty acids.

9. Pharmaceutical formulations according to the preceding claims, in which the active principle is dipyridamole, the gastroresistant polymer is cellulose acetate trimellitate or cellulose acetate phthalate, the swelling polymer is crosslinked sodium carboxymethylcellulose and the gelling hydrophilic matrix is composed of hydroxypropylmethylcellulose.

10. Pharmaceutical formulations according to Claim 9, in which the ratio by weight between active principle/gastroresistant polymer/swelling polymer/gelling hydrophilic polymer is approximately 1:2:1:1, respectively.

11. Process for the preparation of the formulations of Claims 1 - 10, which comprises the addition of the hydrophilic polymeric material to a solution of the active principle and of the gastroresistant material in an organic solvent, the subsequent drying of the suspension, grinding and/or granulation and formulation of the pellets thus obtained in a hydrophilic or lipophilic matrix.

12. Process according to Claim 11, characterised in

that the solution is added to the hydrophilic polymeric material maintained in suspension in an air jet, and the resulting moist product is dried in the same fluid bed.

13. Process according to Claim 11 or 12, characterised in that the active principle and the gastroresistant material are separately dissolved in different solvents and are then loaded onto the hydrophilic material separately or at the same time.

14. Process according to Claim 13, characterised in that the loading operation is carried out using moistening and granulation, topogranulation, spherogranulation, rotogranulation or extrusion techniques.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 92/01503

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K9/16; A61K9/20

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X Y	EP,A,0 271 193 (EUROCELTIQUE SA) 15 June 1988 see page 4, paragraph 4 - page 5, paragraph 4 see page 11 - page 12; example 3	1,4,7 8
Y	EP,A,0 168 044 (FUJISAWA PHARMACEUTICAL CO ,LTD) 15 January 1986 see page 5, line 1 - page 6, line 20 see page 9 - page 10; example 1	8
X Y	EP,A,0 280 571 (ELI LILLY AND COMPANY) 31 August 1988 see page 2, line 38 - line 46 see page 3, line 16 - line 51 see page 4, line 26 - line 50 see page 7 - page 8; example 3 see claim 1	1,3-6,11 2-4

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° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
28 OCTOBER 1992	20. 11. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	BOULOIS D.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

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The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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